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HORMONE COMPOSITION

The present invention r lates to a composition containing oestrogen, which is to be administered vaginally.

BACKGROUND OF THIS INVENTION

Vaginal atrophy can occur in postmenopausal woman and estrogen deprived women who actually do not need any systemic hormone replacement therapy but just local therapy. Consequently, local, topical treatment is preferred in order to avoid the systemic side effects due to long-lasting oestrogen therapy. Local therapy for this purpose has been studied for a long period of time and the hormone has been administered as creams, gels, and silastic rings.

About every second postmenopausal women will experience urogenital discomfort associated with estrogen deficiency. Previous studies have shown that although many of these women use an oral hormone replacement therapy, urogenital symptoms persist.

A composition commonly used is Vagifem® marketed by Novo Nordisk A/S. Vagifem is developed to treat estrogen deficiency-deprived atrophic vaginitis. Vagifem is a small tablet containing 25 μg 17β-estradiol. A usual treatment is one tablet daily for the first 2 weeks of-treatment and, thereafter, one tablet twice a week. Conveniently, Vagifem is administered by placing a tablet at the top of a slim-line pencil-like disposable applicator. By introducing the applicator to the vagina, the Vagifem tablet will, due to the adhesive characteristics of Vagifem, stay in the vagina.

SUMMARY OF THIS INVENTION

One object of this invention is to furnish a hormone composition which gives a clinical effect on vaginal symptoms which is as good as that obtained by administration of Vagifem twice weekly.

A further object of this invention is to furnish a hormone composition furnishing no or only inferior systemic absorption.

A still further object of this invention is to furnish a hormone composition furnishing significant improvement in the vaginal mucosa.

A still further object of this invention is to furnish a hormone composition furnishing no or only inferior systemic effect.

A still further object of this invention is to furnish a hormone composition furnishing low absorption of estrogen.

A still further object of this invention is to furnish a hormone composition furnishing low serum concentration of estradiol.

A still further object of this invention is to furnish a hormone composition furnishing no or only inferior accumulation of circulating estradiol.

A still further object of this invention is to furnish a hormone composition furnishing positive effects on an atrophic vaginal epithelum.

A still further object of this invention is to furnish a hormone composition furnishing complete or substantial vaginal maturation.

A still further object of this invention is to furnish a hormone composition furnishing a reduced risk of osteporosis.

A still further object of this invention is to furnish a hormone composition furnishing increases in percentage of superficial vaginal cells.

A still further object of this invention is to furnish a hormone composition which can be used for the treatment of atrophic vaginitis.

A very specific object of this invention is to furnish a hormone composition furnishing all or most of the following characteristics: Relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and improved cytologic maturation of both the vaginal and urethral mucosa.

DETAILED DESCRIPTION OF THIS INVENTION

The vaginal symptoms treated by the use according to the present invention are dryness, soreness, irritation, and dyspareunia. The urogenital health is characterized by secretions, epithelial integrity, surface thickness, and the pH value of the vagina.

Surprisingly, it has been found that the use according to the claims below have pharmaceutical and clinical advantages compared with the known uses of similar compositions.

It is often recommended to proceed the use according to the claims below with a treatment with a somewhat higher dosage of an estrogen, for example, estradiol. Such a treatment is

herein designated a pre-treatment. In a preferred embodim nt, this pre-treatment is the daily treatment with the same dose as that used for a bi-weekly use according to the claims below.

The compositions used according to this invention may be prepared analogously to the preparation of similar compositions, for example, Vagifem. The compositions used according to this invention may contain any constituent used or suggest to be used in similar compositions. The compositions used according to this invention may be administered analogously with the administration of similar compositions. All these aspects are known to the skilled art worker.

The present invention is further illustrated by the following example which, however, is not to be construed as limiting the scope of protection. Also, the present invention is further illustrated at pages 1-22 below being a part of this description. These additional pages are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description, in the following examples and at pages 1-22 below may, in any combination thereof, be material for realising the invention in diverse forms thereof.

Example 1

58 postmenopausal women were treated with tablets containing either 10 or 25 μg 17β-estradiol. The women inserted 1 tablet intravaginally, once daily for the initial 2 weeks of the study and then twice per week (Sunday & Thursday) for the following 10 weeks. Hence, some of the women only received tablets containing 10 μg 17β-estradiol and the remaining women only received tablets containing 25 μg 17β-estradiol. The estradiol profile when administering 25 or 10 μg 17β-estradiol was similar after the first dose (zero weeks of treatment) and after the above continuous treatment with 25 or 10 μg 17β-estradiol twice weekly for 10 weeks.

CLAIMS

1. The use of an oestrogen in the manufacture of a composition containing oestrogen for the treatment of atrophic vaginitis in woman, by administering weekly an amount of about 10 to about 30 µg estradiol to a woman.

2. The use according to claim 1, wherein the women treated are menopausal or post-menopausal women.

3. The use according to any one of the preceding claims, wherein the weekly amount of about 15 to about 25 µg estradiol.

4. The use according to any one of the preceding claims, wherein daily about 1.5 to about 4 µg estradiol is administered.

5. The use according to any one of the preceding claims, wherein daily about 2 to about 3 µg estradiol is administered.

6. The use according to any one of the preceding claims, wherein twice weekly about 5 to about 15 µg estradiol is administered.

7. The use according to any one of the preceding claims, wherein twice weekly about 7 to about 13 µg estradiol is administered.

8. The use according to the preceding claim, wherein twice weekly about 9 to about 11 µg estradiol is administered.

9. The use according to any one of the preceding claims, wherein no progestogen is administered.

10. The use according to any one of the preceding claims, wherein the composition is to be administered vaginally.

11. The use according to any one of the preceding claims, wherein it is used for a period of time of more than 2 weeks, preferably more than 1 month, more preferred more than 2 months, and even more preferred more than 3 months.

12. A method of treating atrophic vaginitis, comprising administering a composition as described in any of the previous use claims.

13. Any novel feature or combination of features described herein.

Novo Nordisk A/S

Estradiol Absorption in Postmenopausal Women Treated with Low-dose 17 β-Estradiol Vaginal Tablets

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Running foot: Estradiol absorption

PRECIS

Treatment of atrophic vaginitis with low-dose 17 β-estradiol tablets results in consistent, low absorption of estradiol without accumulation.

ABSTRACT

Objectives: The vaginal absorption of estradiol (E2) was evaluated and two low doses of 17 β-E2 (25 μg and 10 μg) were compared in postmenopausal women with atrophic vaginitis.

Design: In a double-blind, randomized, parallel-group study, 58 postmenopausal women were treated with either 25 or 10 μg 17 β-E2 for 12 weeks. Serum E2 and FSH concentrations were measured throughout the study at specified intervals. The area under the curve, maximal concentration, and time to maximal concentration were determined for serum E2 concentrations. Maturation values of vaginal mucosal cells were assessed as an indicator of changes in the condition of the vaginal mucosa in response to treatment.

Results: For both treatment groups, the E2 profiles were similar at weeks 0 and 12. The mean E2 concentrations, areas under the curve, and maximal concentrations were higher in the 25-μg 17 β-E2 group than in the 10-μg 17 β-E2 group. For the majority of patients in each treatment group, the areas under the curve remained below 600 pg·hr/mL at each time point, and the mean FSH concentrations were in the normal postmenopausal range. Patients in each treatment group showed significant improvement ($P \leq .01$) in the condition of the vaginal mucosa.

Conclusion: Treatment with either 25- or 10-μg 17 β-E2 vaginal tablets resulted in improvements in the vaginal mucosa and low absorption of estrogen without the systemic effects often associated with ERT. After 12 weeks of therapy for atrophic vaginitis, absorption patterns remained consistent, and patients did not experience an accumulation of circulating E2.

INTRODUCTION

Over 50% of postmenopausal women will experience urogenital discomfort associated with estrogen deficiency.[1,2] Previous studies have shown that although many of these women use an oral hormone replacement therapy, urogenital symptoms persist.[2] Many of these women may obtain additional benefits from local therapy.

Vaginal administration of low-dose estradiol (E2) tablets offers a safe and convenient method for local relief of vaginal symptoms.[1,3,4] Vaginal administration of estrogen is often more effective in relieving urogenital symptoms than conventional oral ERTs since (1) first pass liver metabolism is avoided and (2) vaginal tissues have an increased sensitivity to estrogen. These characteristics make it possible to use significantly lower doses of estrogen with local therapy compared to oral therapy.

Studies have shown that vaginal ERT preparations can result in rapid and efficient absorption of E2 into systemic circulation.[5,6] However, low-dose preparations that contain 10 and 25 μg E2 effectively relieve the symptoms of atrophic vaginitis without unwanted systemic side effects.[3,6] A low-dose (25 μg) 17 β-E2 vaginal tablet (Vagifem®; Novo Nordisk, Denmark) has been developed to treat estrogen deficiency–derived atrophic vaginitis. These vaginal tablets contain a film-coated hydrophilic cellulose matrix that adheres well to the vaginal mucosa and hydrates slowly to provide a controlled release of E2. They are designed to provide estrogenization of the vaginal mucosa while preventing significant increases in serum estrogen concentrations.

In this study, the vaginal absorption of E2 was evaluated and two low doses of 17 β-E2 (25 μg and 10 μg) were compared in postmenopausal women with atrophic vaginitis.

MATERIALS AND METHODS

This single-center, randomized, double-blind, parallel-group study was conducted in Atlanta, Ga. The study was approved by the appropriate institutional review board, and written informed consent was obtained from each patient. The study was conducted in compliance with the Declaration of Helsinki of 1975, revised in 1983.

In this study, generally healthy, postmenopausal women (hysterectomized or nonhysterectomized), aged 45 years or older, were enrolled. Patients had no more than 5% superficial cells, as assessed by vaginal cytology evaluation, and serum E2 concentrations no greater than 20 pg/mL. Nonhysterectomized patients had endometrial thicknesses no greater than 4 mm, as determined by pelvic ultrasound. Patients with known or suspected history of breast cancer or other hormone-dependent tumors, acute thrombophlebitis or thromboembolic disorders associated with previous estrogen use, or vaginal infection requiring further treatment (at baseline) were excluded from the study, as were patients with genital bleeding of unknown etiology (within 12 months prior to screening). Patients were not to have used any type of vaginal, oral, or vulvar preparations within 7 days prior to screening; any exogenous corticosteroid or sex hormones within 8 weeks prior to baseline; any investigational new drug within the past 30 days; or diethylstilbestrol.

After the screening visit, patients received no study treatment during the 4-week run-in period prior to the baseline visit. At the baseline visit, patients were randomized to receive vaginal tablets containing either 25 or 10 μg 17 β-E2 on a 1:1 basis using a computer-generated scheme. The vaginal tablets were identical in appearance. Patients inserted 1 tablet intravaginally, once daily for the initial 2 weeks of the study and then twice per week (Sunday and Thursday) for the remaining 10 weeks. Patients were instructed to use their medication at a consistent time each

day, preferably in the morning. After the baseline visit, patients returned to the clinic at weeks 1, 2, 4, 8, and 12 for measurements of serum E2 and FSH, as well as assessments of vaginal cytology.

Upon presentation to the clinic for each visit, a vaginal cytology specimen was obtained. Patients then inserted the tablets. Blood samples were drawn 30 minutes before tablet insertion, and at 1, 2, 4, 5, 6, 7, 8, 10, 12, and 24 hours after insertion to determine the serum E2 concentration via radioimmunoassay. The blood samples obtained at 30 minutes before insertion, and at 6, 12, and 24 hours after insertion were also used to determine the FSH concentration via immunoradiometric assay.

The maturation value of vaginal mucosal cells was calculated from the percentages of parabasal, intermediate, and superficial cells according to the following equation:

$$\text{maturation value} = 0 \times [\text{parabasal cells, \%}] + 0.5 \times [\text{intermediate cells, \%}] + 1.0 \times [\text{superficial cells, \%}]$$

The pharmacokinetic parameters of area under the concentration-time curve from 30 minutes before tablet insertion to 24 hours after tablet insertion, maximal concentration, and time to maximal concentration were determined for serum concentrations of E2. Data for area under the curve and maximal concentration were converted to a logarithmic scale, and changes from first dose (at the baseline visit) in the logarithmic values were estimated using 95% confidence intervals derived from paired t-tests. Differences between treatment groups in the degree of absorption of E2 were determined using 95% confidence intervals derived from two sample t-tests based on the observed mean values of the logarithms of area under the curve and maximal concentration. Differences within treatment groups in FSH concentration were determined using the Wilcoxon signed rank test based on changes from baseline in mean concentrations at weeks 2

and 12. Mean concentrations were defined as the average concentrations obtained at 30 minutes before tablet insertion and 6, 12, and 24 hours after insertion. Baseline concentrations for E2 and FSH were defined as the values observed at 30 minutes before tablet insertion at the baseline visit.

This manuscript presents data for the evaluable patient population, which was defined as those patients who had serum E2 concentrations below 20 pg/mL at baseline and who had complete data available at the baseline visit and weeks 2 and 12.

RESULTS

A total of 58 women were treated with vaginal tablets containing either 25 μg 17 β-E2 (28 women) or 10 μg 17 β-E2 (30 women). Ten women discontinued prematurely from the study: 6 in the 25-μg 17 β-E2 group (1 due to an adverse event, 2 due to noncompliance with the protocol, 2 due to the inability of site personnel to obtain venous samples, and 1 due to an ongoing vaginal infection) and 4 in the 10-μg 17 β-E2 group (1 due to noncompliance with the protocol, 1 due to the inability of site personnel to obtain a venous sample, 1 due to relocation, and 1 due to elective surgery). The evaluable patient population consisted of 42 women; 19 women received 25 μg 17 β-E2, and 23 women received 10 μg 17 β-E2. Demographic and baseline characteristics for the evaluable patient population are presented in Table 1. Patient characteristics were similar between treatment groups, with the exception of percentage of parabasal cells at baseline, which was significantly lower for patients in the 25-μg 17 β-E2 group compared to those in the 10-μg 17 β-E2 group ($P = .027$, t-test).

The 24-hour concentration profiles for serum E2 at weeks 0 and 12 are presented in Figures 1 and 2, respectively, and the associated pharmacokinetic characteristics are presented in Table 2. At weeks 0 and 12, the serum E2 profiles were similar within each treatment group. The serum

E2 concentrations, as well as the corresponding mean area under the curve and maximal concentration, were higher for patients who received 25 μg 17 β-E2 than for patients who received 10 μg 17 β-E2. The average serum E2 concentrations over 24 hours were also higher in the 25-μg 17 β-E2 group than in the 10-μg 17 β-E2 group.

A comparison between the areas under the curve for serum E2 at weeks 0 and 12 is presented in Figure 3. The majority of patients in each treatment group had areas under the curve below 600 pg·hr/mL at both time points (14 patients [74%] and 22 patients [96%] in the 25- and 10-μg 17 β-E2 groups, respectively). A comparison between area under the curve for serum E2 and mean FSH concentration at week 12 is presented in Figure 4. At week 12, the majority of patients in each treatment group had mean FSH concentrations in the normal postmenopausal range (at least 35 pg/mL); 3 patients in the 25-μg 17 β-E2 group had mean FSH concentrations below 35 pg/mL.

The mean maturation value and mean change from baseline in maturation value are presented in Table 3. In each treatment group, patients experienced a significant increase in maturation value over baseline values ($P \leq .001$ at weeks 1 and 2, and $P \leq .01$ at week 12; 2-tailed, paired t-test). At all time points, mean maturation values and mean changes from baseline in maturation value were comparable between treatment groups. A comparison between the area under the curve for serum E2 and the maturation value at week 12 is presented in Figure 5. The majority of patients in each treatment group (13 patients [68%] and 14 patients [64%] in the 25- and 10-μg 17 β-E2 groups, respectively) showed increases in maturation values from the corresponding baseline values (53.4 and 51.0 in the 25- and 10-μg 17 β-E2 groups, respectively).

DISCUSSION

Atrophic vaginitis and other forms of urogenital discomfort due to estrogen deficiency will affect over 50% of postmenopausal women.[1,2] Previously, these conditions were commonly treated with systemic hormone replacement therapy. Recently, low-dose therapies that deliver estrogen directly to the vaginal tissue have provided alternative therapeutic options. The optimum intravaginal therapy will provide consistent estrogen absorption with adequate relief of vaginal symptoms without systemic absorption and the associated side effects.[3,6] The low-dose vaginal tablets used in this study meet these criteria.

This study examined the systemic absorption of E2 in patients who received treatment with either 25- or 10-μg 17 β-E2 vaginal tablets for 12 weeks. The majority of patients in each treatment group (74% in the 25-μg 17 β-E2 group and 96% in the 10-μg 17 β-E2 group) experienced low systemic absorption of E2 at both the beginning and end of the 12-week treatment period, as indicated by areas under the serum E2 concentration curve below 600 pg·hr/mL at each time point. Of the 6 remaining patients, 4 who did experience higher E2 absorption at week 12 also had areas under the curve greater than 600 pg·hr/mL at both week 0 and 12, suggesting that these patients were characteristically high E2 absorbers. It is likely that these patients would experience greater absorption of E2 as a result of any ERT.

The 24-hour serum E2 profiles at weeks 0 and 12 were similar for each treatment group, again indicating that overall, women had consistent E2 absorption patterns at the beginning and end of the treatment period. The average E2 concentrations at each time point were within the normal postmenopausal range (normal postmenopausal range for E2 concentration: ≤40 pg/mL). In contrast, other studies have reported marked decreases in E2 absorption with ERT. These decreases are often attributed to saturation of the E2 receptors during vaginal maturation.[3] While

vaginal administration of estrogen is often used to treat atrophic vaginitis, the exact mechanism for E2 absorption through the vagina has not been clearly defined. The promising results from this study demonstrated consistent E2 absorption over 12 weeks of treatment. However, only long-term therapy will maintain the health of the vaginal tissue, and further extended studies are needed.

The biologic efficacy of absorbed E2 may vary among patients. Although patients may be relatively high E2 absorbers, the biologic potency may be reduced (eg, by binding to serum hormone-binding globulin), and these patients may not demonstrate marked FSH suppression. In this study, after 12 weeks of treatment with either 25 or 10 μg 17 β-E2, FSH concentrations were rarely suppressed to premenopausal levels, suggesting that the observed increase in serum E2 concentration is not associated with clinically significant systemic E2 potency. The E2 and FSH concentrations reported in this study are consistent with results from an independent study in which patients received either 25-μg 17 β-E2 tablets or 1.25-mg conjugated equine estrogen cream (Premarin®; Wyeth-Ayerst, Philadelphia, PA). Over this 6-month study, significantly fewer patients who received 25-μg 17 β-E2 tablets compared to those who received the vaginal cream experienced E2 or FSH concentrations outside the normal postmenopausal ranges (normal postmenopausal ranges in the 6-month study: E2 concentration, ≤49 pg/mL; FSH concentration; ≥35 IU/L).[7] In this same study, the likelihood of endometrial hyperplasia was also reduced in patients treated with 25-μg 17 β-E2 tablets compared to those treated with vaginal cream.

The maturation value measures the effect of the absorbed estrogen and provides a quantitative assessment of the condition of the vaginal mucosa. Patients in each treatment group showed significant improvement ($P \leq .01$) in the condition of the vaginal mucosa as indicated by increases in maturation value. After 12 weeks of treatment, the majority of patients (over 60%)

in each treatment group had increased maturation values, indicating improvement in vaginal health. Although both the 25- and 10-μg 17 β-E2 dose levels demonstrated positive effects on an atrophic vaginal epithelium while maintaining low serum concentrations of E2, a relationship between increased maturation values and E2 blood levels could not be discerned. Thus, although E2 absorption is important, it is not necessarily indicative of the clinical effect of ERT. The improvement in vaginal health may be due to direct perfusion and/or lymphatic absorption of the local E2 through the vaginal epithelium. In this study, vaginal maturity was measured exclusively with the maturation value. Since the vaginal response is likely due to enhanced glycogenization and acidification of the vagina, monitoring the vaginal pH would provide another useful measure of vaginal health.[8,9]

Although vaginal maturation with low concentrations of circulating E2 is a primary treatment goal of local vaginal ERT, other independent studies have also associated vaginally-administered ERT with maturation of the urethral epithelium[3]. Reduced risks of osteoporosis in postmenopausal women have also been observed.[10,11,12] These benefits likely rely on the concentration of circulating E2 added to the endogenous production of E2 in bone, which is especially true in older, natural postmenopausal women.[10] Since the average serum E2 concentrations were higher for patients who recieved 25 μg 17 β-E2 than for those who received 10 μg 17 β-E2, it is possible that patients who receive the higher dose may derive additional benefits in increased bone strength while maintaining serum E2 concentrations within a physiologic (perimenopausal) range.

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Table 1. Demographic and Baseline Characteristics (Evaluable Patients)

Characteristic	Treatment group: 25 μg 17 β-E2 (N = 19)	10 μg 17 β-E2 (N = 23)
Age (yr)[a]	52.1 ± 5.6 (45-63)	54.8 ± 5.1 (48-69)
Race		
Caucasian	16 (84.2%)	18 (78.3%)
Other	3 (15.8%)	5 (21.7%)
Time since last menses (yr)[a]	10.7 ± 7.6 (1-25)	14.3 ± 8.7 (1-32)
Hysterectomized		
Yes	12 (63.2%)	17 (73.9%)
No	7 (36.8%)	6 (26.1%)
E2 concentration at screening (pg/mL)[a]	7.0 ± 2.8 (3-13)	7.6 ± 3.7 (2-18)
Vaginal cytology at screening		
Parabasal cells (%)[a]	1.9 ± 2.5[b] (0-7)	8.4 ± 12.9[b] (0-48)
Intermediate cells (%)[a]	95.2 ± 7.8 (65-100)	90.1 ± 12.4 (51-100)
Superficial cells (%)[a]	2.9 ± 8.0 (0-35)	1.5 ± 1.7 (0-6)

SD = standard deviation; E2 = estradiol

[a] Data presented as mean ± SD (range).

[b] Statistically significant; $P = .027$ (t-test)

Table 2. Pharmacokinetic Parameters for 24-Hour Serum Estradiol Profiles (Evaluable Patients)

Time point	Pharmacokinetic characteristic	Treatment group: 25 μg 17 β-E2 (N = 19)	Treatment group: 10 μg 17 β-E2 (N = 23)
Week 0			
	Area under the curve (pg·hr/mL)[a]	538 ± 265	349 ± 107
	Maximal concentration (pg/mL)[a]	51 ± 34	35 ± 17
	Time to maximal concentration (hr)[a]	15 ± 9	9 ± 5
	Serum concentration over 24 hours (pg/mL)	22	15
Week 12			
	Area under the curve (pg·hr/mL)[a]	563 ± 341	264 ± 120
	Maximal concentration (pg/mL)[a]	49 ± 27	22 ± 17
	Time to maximal concentration (hr)[a]	13 ± 6	10 ± 8
	Serum concentration over 24 hours (pg/mL)	23	11

E2 = estradiol; SD = standard deviation

[a] Data presented as mean ± SD.

Table 3. Mean Maturation Values and Changes From Baseline (All Patients)

		Treatment group		
Time point	N	25 μg 17 β-E2	N	10 μg 17 β-E2
Week 0				
Mean ± SD	25	52.4 ± 7.1	28	51.0 ± 6.2
Week 12				
Mean ± SD	20	58.4 ± 7.5	23	62.2 ± 15.7
Mean change ± SD	20	7.0 ± 8.7[b]	23	11.2 ± 17.8[b]

SD = standard deviation

[a] Statistically significant; $P \leq .001$ (2-tailed, paired t-test)

[b] Statistically significant; $P \leq .01$ (2-tailed, paired t-test)

Figure 1. Serum concentrations of estradiol at week 0.

---□--- 25 μg 17-β E2 — — 10 μg 17-β E2

Figure 2. Serum concentrations of estradiol at week 12.

---□--- 25 μg 17-β E2 —●— 10 μg 17-β E2

Figure 3. Area under the serum estradiol curve at weeks 0 and 12.

□ 25 μg 17-β E2 ● 10 μg 17-β E2

Figure 4. Area under the serum estradiol curve and serum FSH concentration at week 12.

□ 25 μg 17-β E2 ● 10 μg 17-β E2

Figure 5. Area under the serum estradiol curve and maturation value at week 12.

Maturation values at baseline were 52.4 in the 25-μg 17-β E2 group and 51.0 in the 10-μg 17-β E2 group.

□ 25 μg 17-β E2 ● 10 μg 17-β E2